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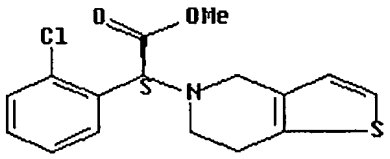
Clopidogrel hydrobromide in crystalline Forms I and II and methods of their preparation

Technical Field

The invention concerns new crystalline forms of the hydrobromide of the (alpha S) alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetic acid methyl ester (thereinafter clopidogrel hydrobromide), which are characterized by X-ray (RTG) diffraction and infrared spectra, and methods of their preparation.

Background Art

The (alpha S) alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetic acid methyl ester, clopidogrel of formula I



I

is an anti-thrombic agent that was described in CZ patent 274 420 (EP 281 459), wherein blood coagulation decreasing activities of various salts of this substance were also demonstrated. Currently sold clopidogrel-based pharmaceutical formulations contain this active agent in the form of its hydrogensulfate salt (HSO_4^- anion). The method of preparation of the S-enantiomer, published in the above-cited patent involves reaction of the racemic mixture with optically active camphorsulfonic acid and subsequent separation of the diastereoisomer.

The respective salt of clopidogrel with camphorsulfonic acid is converted, by a solution of sodium hydrogen carbonate in methylene chloride medium, into an optically active base, which is obtained by evaporation of the solvent.

The evaporation residue of the active base is converted into the respective salt. Specifically, the hydrobromide is obtained by dissolving the base in diethyl or diisopropyl ether and precipitating drop by drop with 48% hydrobromic acid. Drying the formed precipitate affords crystals with the melting point of 111°C .

In the cited patent, toxicity of the hydrobromide is also evaluated, which is even somewhat lower than that of the currently used hydrogensulfate. (LD_{50} of clopidogrel hydrogen sulfate is 2,591 mg and LD_{50} of clopidogrel hydrobromide is 4,268 mg).

Disclosure of Invention

The new crystalline Form I of clopidogrel hydrobromide is characterized by interplanar distances ascertained by X-ray diffraction, d: 4.01 Å; 4.39 Å and 3.17 Å, or by infrared spectrogram with bands at 1743; 1421; 1237, 760 and 728 cm^{-1}.

The new crystalline Form II of clopidogrel hydrobromide is characterized by interplanar distances ascertained by X-ray diffraction, d: 4.52 Å; 3.83 Å; 3.48 Å, or by infrared spectrogram with bands at 1754; 1436; 1317 and 1223 cm^{-1}.

The crystalline Form I can be obtained from a solution of the base in toluene by precipitating with 48% hydrobromic acid. This procedure yields first an oily emulsion of the hydrobromide in toluene, which is, however, with further stirring converted into a crystalline matter. Stirring can be performed at room temperature but it is also possible to decrease the temperature gradually.

A preferable method of preparation of crystalline form I involves adding a 48% solution of hydrobromic acid in water to a solution of 5 to 15% of the clopidogrel base in toluene, whereas the molar ratio of the clopidogrel base and hydrogen bromide is 1 : 0.9 to 1.5.

Form II can be obtained by reaction of a solution of the clopidogrel base in an organic solvent, e.g. ethyl acetate or toluene, with a solution of hydrobromic acid in toluene. Crystalline Form II gradually matures at decreased temperature, i.e. precipitation is performed preferably at temperatures 0 to 30°C and crystals grow preferably at temperatures lower than 10°C. The method preferably involves using a solution of the clopidogrel base having a

concentration 5 to 40 weigh % and precipitating it with a solution of hydrogen bromide in toluene of concentrations 5 to 15 weight %, whereas the molar ratio of the clopidogrel base and hydrogen bromide is 1 : 0.9 to 1.1.

Melting points of both forms are difficult to reproduce and identification fails. They range between about 113 and 140°C.

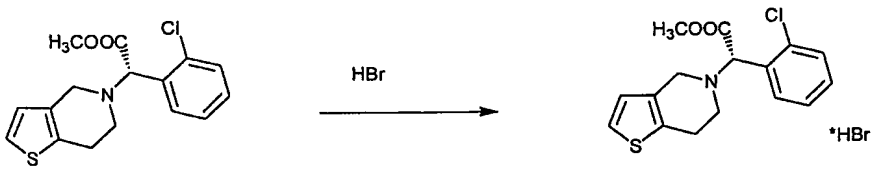
Brief Description of Drawings

Figure 1 shows infrared spectra of clopidogrel hydrobromide Form I.
Figure 2 shows infrared spectra of clopidogrel hydrobromide Form II.
Figure 3 shows an X-ray diffraction pattern of clopidogrel hydrobromide Form I.
Figure 4 shows an X-ray diffraction pattern of clopidogrel hydrobromide Form II.

The invention is elucidated by the following examples, which have purely illustrative character and do not limit the extent of the invention in any respect.

Examples

Scheme



(I) (II)

Example 1

3.38 g (0.0105 mol) of the clopidogrel base of formula (I) are dissolved in 10 ml of toluene at room temperature. A solution of HBr in toluene (11.5 ml of the solution containing 0.86 g of HBr) is added at once under stirring. The resulting precipitate is stirred at room temperature for 1 hour. After this time, the reaction mixture is left sitting at temperature +6°C for 4 hours. The precipitate is sucked off and washed with toluene. After air drying, 2.9 g of yellowish crystals of hydrobromide of formula (II) (69%) are obtained, having the melting point 132 to

138°C. The crystals were characterized by an X-ray diffraction pattern and infrared spectra as the crystalline Form II (Figure 2).

The results of the X-ray diffraction were converted into interplanetary distances D:

2θ[deg]	d [Å]	I	I/I0
11.20	9.1631	141.00	20.84
11.45	8.9654	149.01	22.02
12.20	8.416	92.29	13.64
13.30	7.7222	71.52	10.57
15.10	6.8096	137.52	20.32
16.11	6.3826	161.60	23.88
17.58	5.8541	88.96	13.15
18.84	5.4651	78.63	11.62
19.75	5.2163	145.54	21.51
22.82	4.522	676.62	100.00
24.41	4.2313	261.39	38.63
25.50	4.0526	104.53	15.45
26.97	3.8363	422.01	62.37
29.20	3.5489	217.39	32.13
29.74	3.4851	289.33	42.76
32.08	3.2375	168.90	24.96
33.61	3.0935	163.74	24.20
37.76	2.7644	175.01	25.87

Example 2

6.1 g (0.0189 mol) of the clopidogrel base of formula (I) are dissolved in 60 ml ethyl acetate at room temperature. The solution is cooled down in a water-ice bath to temperature +5°C and 20.8 ml of solution of HBr in toluene is added drop by drop within 0.5 hours at this temperature. The mixture of crystals in toluene is stirred for another 2 hours at temperature 0 to +5°C. The resulting crystalline fraction is sucked off and washed with ethyl acetate. After air drying, 3.7 g of cream-coloured crystals of the hydrobromide of formula (II) (54.2%) were

obtained, having the melting point 135 to 139°C. The crystals were characterized by an X-ray diffraction pattern (Figure 4) and infrared spectra as the crystalline Form II.

Example 3

6.88 g (0.02137 mol) of the clopidogrel base of formula (I) are dissolved in 100 ml toluene at room temperature. At this temperature, 2.25 ml of 48% HBr is added to the solution drop by drop. An oily matter precipitated out of the solution, which crystallized after 4 hours of stirring at room temperature. The resulting crystals were sucked off and washed with toluene. After air drying, 6.66 g of yellowish crystals of the hydrobromide of formula (II) (77.4%) were obtained, having the melting point 120 to 134°C. The crystals were characterized by an X-ray diffraction pattern (Figure 3) and infrared spectra as the crystalline Form I (Figure 1).

The crystals provided the following X-ray diffraction pattern:

2θ [deg]	d [Å]	I	I/I0
10.65	9.64	71.07	16.65
11.53	8.90	66.64	15.61
14.70	6.99	250.69	58.73
16.30	6.31	103.94	24.35
18.70	5.50	227.88	53.39
19.56	5.27	92.56	21.68
21.12	4.88	113.71	26.64
22.11	4.66	63.85	14.96
23.06	4.47	96.56	22.62
23.52	4.39	422.71	99.03
24.08	4.29	256.23	60.03
25.26	4.09	108.85	25.50
25.79	4.01	426.86	100.00
26.18	3.95	61.00	14.29
27.40	3.78	150.10	35.16
28.39	3.65	196.78	46.10
28.90	3.58	116.94	27.40
29.86	3.47	90.02	21.09

30.94	3.35	154.84	36.27
32.73	3.17	337.56	79.08
33.37	3.12	287.31	67.31
36.33	2.87	73.66	17.26
36.76	2.84	98.37	23.05
37.71	2.77	147.66	34.59
39.12	2.67	120.60	28.25

Example 4

21.48 g (0.0667 mol) of the clopidogrel base of formula (I) were dissolved in 312 ml toluene at room temperature. The resulting solution is cooled down in a water-ice bath to temperature +5°C. At this temperature, 7 ml of 48% HBr in toluene is added drop by drop within 10 minutes. The reaction mixture is then tempered to temperature 18 to 20°C and stirred at this temperature for 3 hours. The resulting crystals are sucked off, washed with toluene and air dried at room temperature. 19.46 g of yellowish crystals of the hydrobromide of formula (II) (72.4%) are obtained, having the melting point 113-120°C. The resulting crystals were characterized with an X-ray diffraction pattern and infrared spectra as the crystalline Form I.

Melting points were measured at Kofler's block.

CLAIMS

1. Clopidogrel hydrogenbromide in the crystalline Form I characterized by an X-ray diffraction pattern with characteristic interplanar distances d of 4.01; 4.39 and 3.17 Å.

2. Clopidogrel hydrobromide in the crystalline Form I according to claim 1 characterized by interplanar distances d of 3.12; 6.99; 5.5; 4.29 and 3.65 Å.

3. Clopidogrel hydrobromide in the crystalline Form I according to claims 1 or 2 characterized by bands in the infrared spectra at 1743; 1421; 1237, 760 and 728 cm^{-1}.

4. Clopidogrel hydrobromide in the crystalline Form II characterized by an X-ray diffraction pattern with characteristic interplanar distances d of 4.52; 3.83; 3.48 Å.

5. Clopidogrel hydrobromide in the crystalline Form II according to claim 4 characterized by interplanar distances d of 6.38; 2.76 and 3.23 Å.

6. Clopidogrel hydrobromide in the crystalline Form II according to claims 4 or 5 characterized by bands in the infrared spectra at 1754; 1436; 1317 and 1223 cm^{-1}.

7. A method of preparation of clopidogrel hydrobromide of the crystalline Form I according to claims 1-3 ***characterized in*** that clopidogrel base dissolved in toluene is precipitated with a concentrated solution of hydrobromic acid.

8. The method of preparation of clopidogrel hydrobromide of the crystalline Form I according to claim 7 ***characterized in*** that after precipitation, the resulting oily matter is mixed with toluene for a time necessary for formation of crystal.

9. The method of preparation of clopidogrel hydrobromide of the crystalline Form I according to claim 7 ***characterized in*** that a 48% solution of hydrobromic acid in water is added to a solution of 5 to 15% of the clopidogrel base in toluene, whereas the molar ratio of the clopidogrel base and hydrogen bromide is 1 : 0.9 to 1.5.

10. The method of preparation of clopidogrel hydrobromide of the crystalline Form II according to claims 4-6 ***characterized in*** that the clopidogrel base is dissolved in an organic solvent and precipitated with a solution of hydrobromic acid in toluene.

11. The method of preparation of clopidogrel hydrobromide of the crystalline Form II according to claim 10 ***characterized in*** that precipitation is performed at temperatures 0 to 30°C and growth crystals occurs at temperatures lower than 10°C.

12. The method of preparation of clopidogrel hydrobromide of the crystalline Form II according to claim 10 ***characterized in*** that a solution of the clopidogrel base having a concentration of 5 to 40 weight% is used and is precipitated with a solution of hydrogen bromide in toluene having a concentration of 5 to 15 weight%, whereas the molar ratio of the clopidogrel base and hydrogen bromide is 1 : 0.9 to 1.1.

Abstract

Title of Invention: Clopidogrel hydrobromide in crystalline Forms I and II and methods of their preparation

The invention concerns clopidogrel hydrogenbromide in the crystalline Form I characterized by an X-ray diffraction pattern with characteristic interplanar distances d of 4.01; 4.39 and 3.17 Å and which is further characterized by bands in the infrared spectra at 1743; 1421; 1237, 760 and 728 cm^{-1}. Clopidogrel hydrobromide in the crystalline Form II is characterized by an X-ray diffraction pattern with characteristic interplanar distances d of 4.52; 3.83; 3.48 Å, as well as bands in the infrared spectra at 1754; 1436; 1317 and 1223 cm^{-1}. The method of preparation of clopidogrel hydrobromide in the crystalline Form I consist in precipitating the clopidogrel base dissolved in toluene with a concentrated solution of hydrobromic acid. The method of preparation of clopidogrel hydrobromide in the crystalline Form II consist in dissolving the clopidogrel base in an organic solvent and precipitating it with a solution of hydrobromic acid in toluene.

Infrared spectra – clopidogrel hydrobromide crystalline Form I

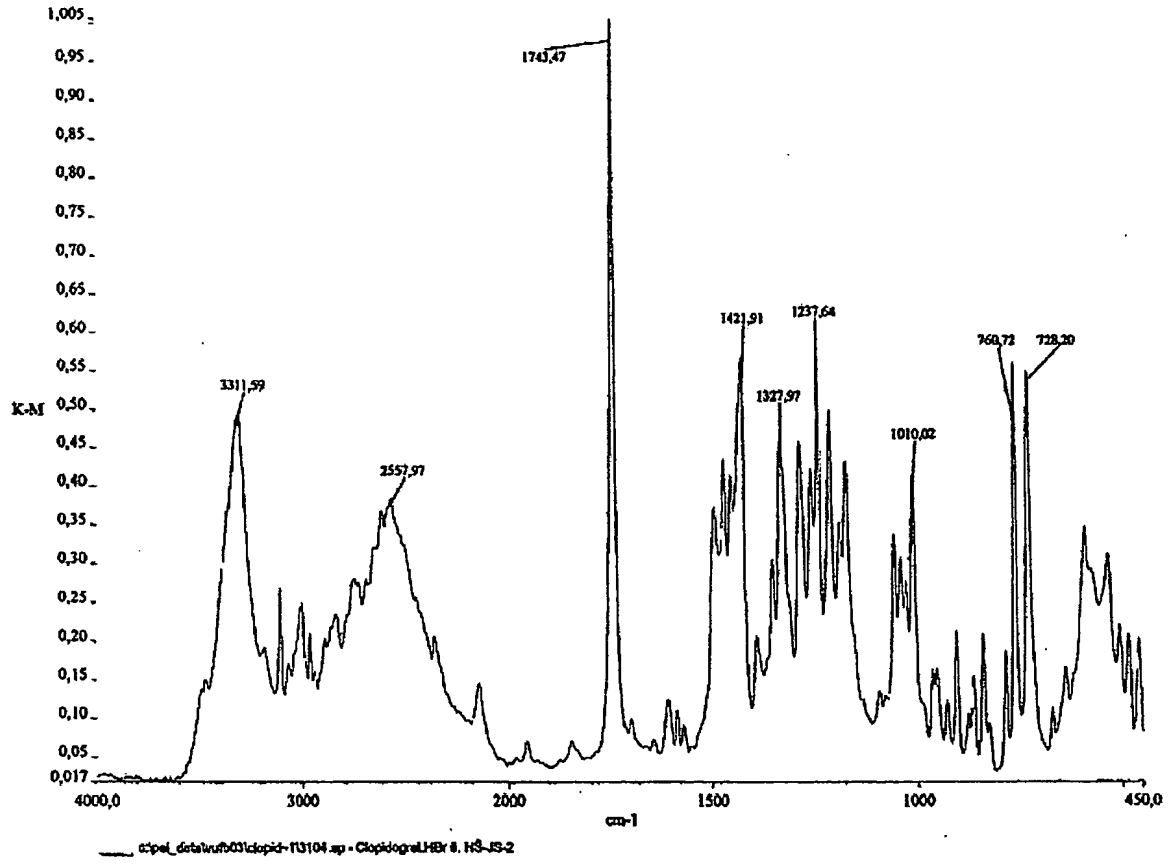


Fig. 1

Infrared spectra – clopidogrel hydrobromide crystalline Form II

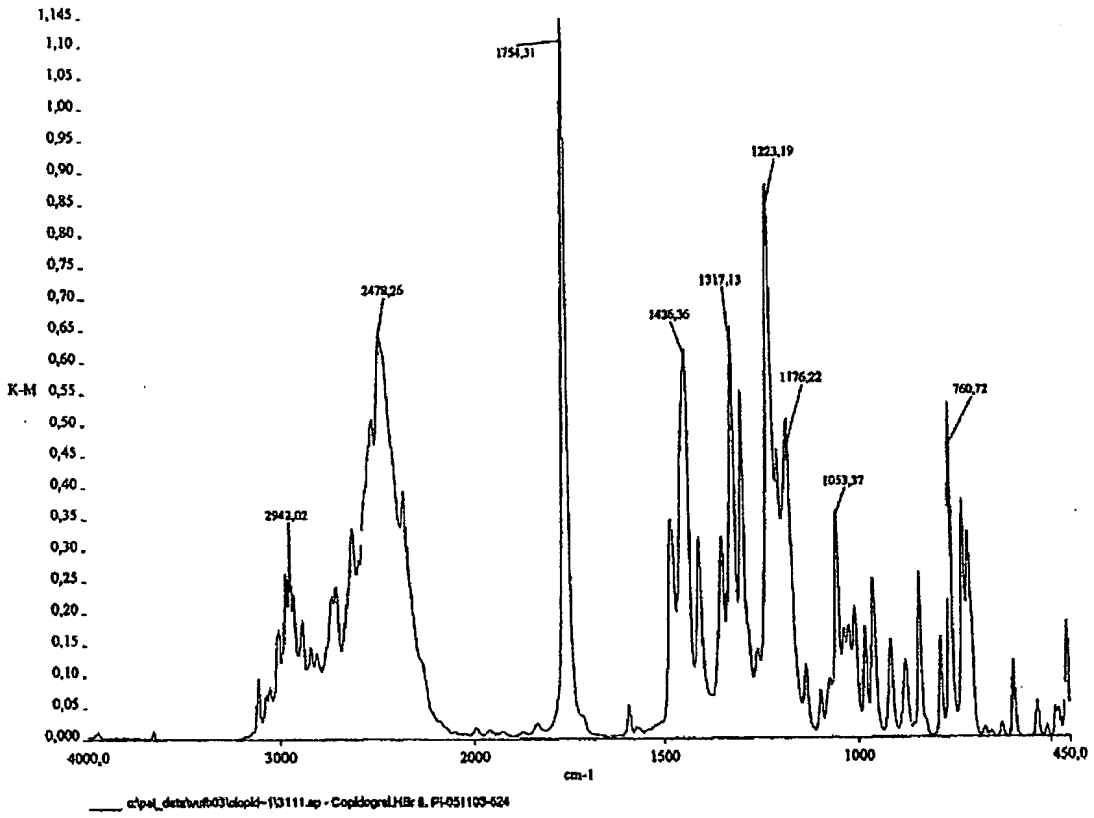


Fig. 2

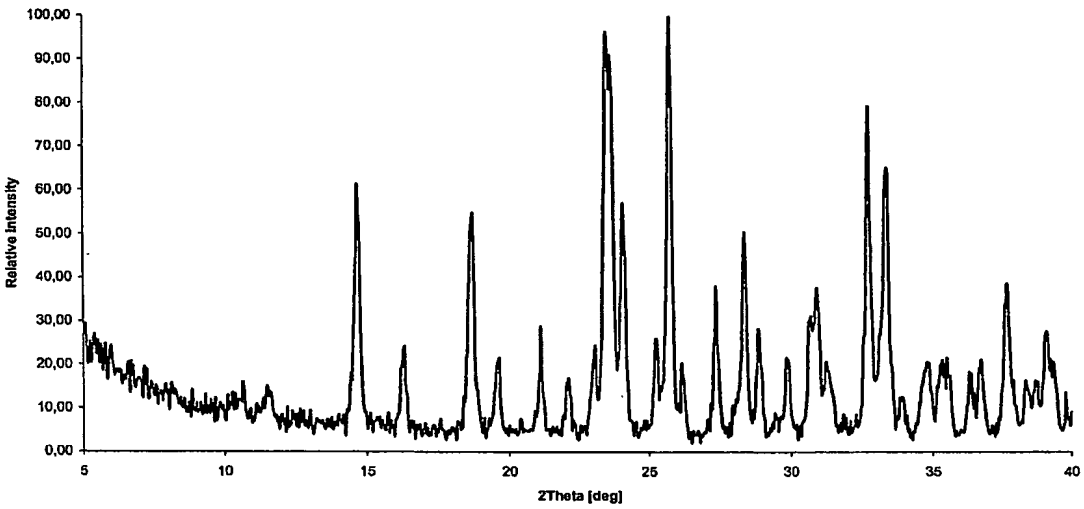

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Fig. 3

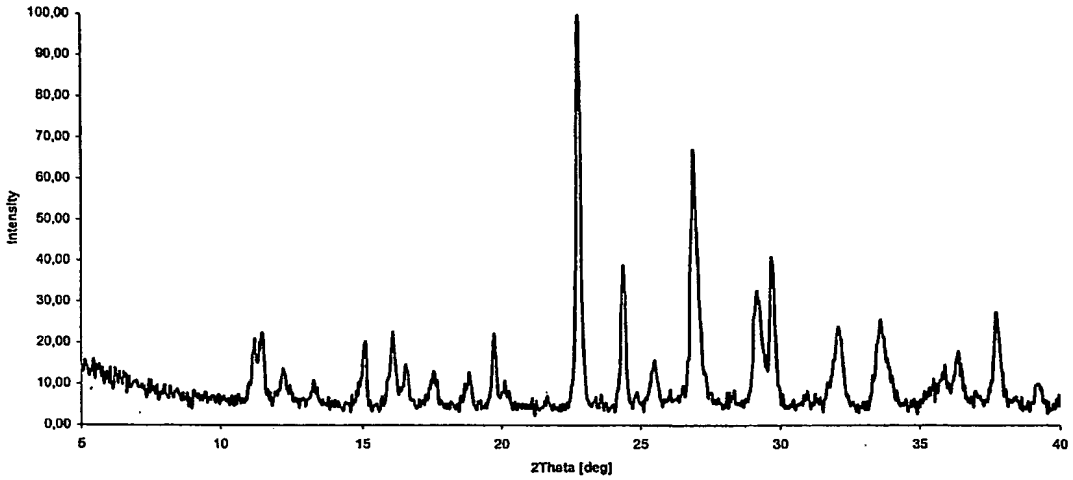
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Fig. 4